9/18/06

L9 ANSWER 1 OF 14 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
AN 2003:326802 BIOSIS
DN PREV200300326802
TI THE CANNABINOID LIGAND AM251 ACTS As AN INVERSE AGONIST AT THE CB1 RECEPTOR IN VITRO, AND INDUCES WEIGHT LOSS IN CAFETERIA DIET - FED MICE IN VIVO.
AU Hjorth, S. [Reprint Author]; Johansson, M. S. [Reprint Author]; Carlsson, K.; Greasley, P. J.
CS Integrative Pharmacology, AstraZeneca R and D, Molndal, Molndal, Sweden
SO Society for Neuroscience Abstract Viewer and Itinerary Planner, (2002) ~~Vol. 2002, pp. Abstract No. 775.17. http://sfn.scholarone.com~~. cd-rom. Meeting Info.: 32nd Annual Meeting of the Society for Neuroscience. Orlando, Florida, USA. November 02-07, 2002. Society for Neuroscience.
DT Conference; (Meeting)
Conference; (Meeting Poster)
Conference; Abstract; (Meeting Abstract)
LA English
ED Entered STN: 16 Jul 2003
Last Updated on STN: 16 Jul 2003
AB AM251 is a close structural (4-iodophenyl) analogue to the reference CB1 receptor inverse agonist SR141716 and is frequently used as an antagonist at the CB1 sites. The present study assessed i) whether the drug is indeed a true CB1 receptor antagonist and, given central CB1 receptor modulation of food intake, ii) if its sub-chronic administration would induce weight loss in obese mice. AM251 was compared with SR141716 with regard to its ability to inhibit GTPgammaS binding mediated by CB1 receptors expressed in HEK293 cells in vitro, and to reduce body weight in cafeteria diet-fed mice. AM251 was approximately 3x less potent than SR141716 (IC50 6.4 and 1.8 nM, respectively) in the GTPgammaS assay, and both agents demonstrated equivalent inverse agonist properties. In vivo, 7 days administration of AM251 or SR141716 (10mg/kg i.p. once daily) resulted in a significant drop in body weight of about 8% from baseline (despite continued access to palatable diet). The response to both compounds in this regard was virtually superimposable. For comparison, untreated and vehicle animals gained apprx5% weight over the same time period. We conclude that AM251 is not an antagonist but rather an inverse agonist at CB1 receptors, displaying slightly lower potency than, but similar efficacy to SR141716. Moreover, both agents induced clear-cut weight loss in cafeteria diet-induced obese mice, thus concurring with the notion that inverse agonism at (central) CB1 receptors affects appetite and/or reward mechanisms and may represent an important exploitable target in the development of novel anti-obesity treatments.
AB. . . antagonist and, given central CB1 receptor modulation of food intake, ii) if its sub-chronic administration would induce weight loss in obese mice. AM251 was compared with SR141716 with regard to its ability to inhibit GTPgammaS binding mediated by CB1 receptors expressed. . . displaying slightly lower potency than, but similar efficacy to SR141716. Moreover, both agents induced clear-cut weight loss in cafeteria diet-induced obese mice, thus concurring with the notion that inverse agonism at (central) CB1 receptors affects appetite and/or reward mechanisms and may represent an important exploitable target in the development of novel anti-obesity treatments.
IT Major Concepts
Behavior; Nutrition; Pharmacology
IT Diseases
obesity: nutritional disease
Obesity (MeSH)
IT Chemicals & Biochemicals
AM251: anorexic-drug, cannabinoid ligand; CB1 receptor; SR14176
RN 51709-03-6Q (AM251)
183232-66-8Q (AM251)

L9 ANSWER 2 OF 14 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
AN 2003:326801 BIOSIS
DN PREV200300326801
TI VOLUNTARY EXERCISE FACILITATES THE EFFECTS OF AM251 ON BODY WEIGHT LOSS IN GENETICALLY OBESE AND WILDTYPE MICE.
AU Zhou, D. [Reprint Author]; Shearman, L. P. [Reprint Author]
CS Department of Pharmacology, Merck Research Laboratories, Rahway, NJ, USA
SO Society for Neuroscience Abstract Viewer and Itinerary Planner, (2002) Vol. 2002, pp. Abstract No. 775.16. http://sfn.scholarone.com. cd-rom. Meeting Info.: 32nd Annual Meeting of the Society for Neuroscience. Orlando, Florida, USA. November 02-07, 2002. Society for Neuroscience.
DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
Conference; (Meeting Poster)
LA English
ED Entered STN: 16 Jul 2003
Last Updated on STN: 16 Jul 2003
AB Central cannabinoid systems are involved in regulation of energy homeostasis. Cannabinoid CB1 receptor inverse agonists suppress appetite and reduce body weight in various species. Exercise enhances fatty acid oxidation and stimulates lipolysis. These studies tested the hypothesis that voluntary running wheel exercise would potentiate the effects of AM251, a CB1 receptor inverse agonist, on food intake and body weight loss in murine models of obesity. ob/ob, A(y)/a (agouti yellow obese), and C57BL/6J mice were treated orally with vehicle, 1, 3 or 10 mg/kg of AM251 one hour before lights off. The suppressive effects of AM251 on overnight food intake (FI), body weight (BW), and water intake (WI) were significant at 3 and 10 mg/kg in ob/ob mice. The high dose (10 mg/kg) of AM251 decreased FI and BW while it did not influence WI in A(y)/a mice. Feeding frequency and duration were suppressed for 4-6 hours following AM251 treatment in ob/ob and A(y)/a mice. AM251 at these doses had no impact on the appetitive behavior or body weight of lean C57BL/6J mice. After a 1-week wash-out period, mice were given running wheels in their home cages and were treated with AM251. When coupled with running wheel access, all animals had increased sensitivity to AM251. AM251 at 1 mg/kg, which did not decrease FI or BW in non-exercising animals, suppressed FI and BW gain in ob/ob mice. Obese A(y)/a and lean C57BL/6J mice with running wheel access lost BW following AM251 (at all doses). Food intake of C57BL/6J mice given running wheels was unchanged. Voluntary exercise can potentiate the effects of AM251 on energy homeostasis and body weight loss in lean and obese mice.
TI VOLUNTARY EXERCISE FACILITATES THE EFFECTS OF AM251 ON BODY WEIGHT LOSS IN GENETICALLY OBESE AND WILDTYPE MICE.
AB . . . the effects of AM251, a CB1 receptor inverse agonist, on food intake and body weight loss in murine models of obesity. ob/ob, A(y)/a (agouti yellow obese), and C57BL/6J mice were treated orally with vehicle, 1, 3 or 10 mg/kg of AM251 one hour before lights off.. . . 1 mg/kg, which did not decrease FI or BW in non-exercising animals, suppressed FI and BW gain in ob/ob mice. Obese A(y)/a and lean C57BL/6J mice with running wheel access lost BW following AM251 (at all doses). Food intake of C57BL/6J. . . was unchanged. Voluntary exercise can potentiate the effects of AM251 on energy homeostasis and body weight loss in lean and obese mice.
IT Major Concepts
Behavior; Metabolism; Nutrition
IT Diseases
obesity: nutritional disease
Obesity (MeSH)
IT Chemicals & Biochemicals
AM251: CB1 receptor agonist
RN 51709-03-6Q (AM251)
183232-66-8Q (AM251)

L9 ANSWER 3 OF 14 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN

AN 2002:529351 BIOSIS
DN PREV200200529351
TI Effect of a 28-d treatment with L-796568, a novel beta3-adrenergic receptor agonist, on energy expenditure and body composition in obese men.
AU Larsen, Thomas M. [Reprint author]; Toubro, Soren; van Baak, Marleen A.; Gottesdiener, Keith M.; Larson, Patrick; Saris, Wim H. M.; Astrup, Arne
CS Research Department of Human Nutrition, Royal Veterinary and Agricultural University, Rolighedsvej 30, 1958, Frederiksberg, Copenhagen, Denmark tml@kvl.dk
SO American Journal of Clinical Nutrition, (October, 2002) Vol. 76, No. 4, pp. 780-788. print.
CODEN: AJCNAC. ISSN: 0002-9165.
DT Article
LA English
ED Entered STN: 16 Oct 2002
Last Updated on STN: 5 Dec 2002
AB Background: Stimulation of energy expenditure (EE) with selective thermogenic beta-adrenergic agonists may be a promising approach for treating obesity. Objective: We analyzed the effects of the highly selective human beta3-adrenergic agonist L-796568 on 24-h EE, substrate oxidation, and body composition in obese, weight-stable men. Design: In this 2-center, double-blind, randomized, parallel-group study, we measured 24-h EE before and after 28 d of treatment with L-796568 (375 mg/d) or placebo during weight maintenance (ie, without dietary intervention) in nondiabetic, nonsmoking men aged 25-49 y with body mass index (in kg/m2) of 28-35 (n=10 subjects per treatment group). Results: The mean change in 24-h EE from before to after treatment did not differ significantly between groups (92+-586 and 86+-512 kJ/24 h for the L-796568 and placebo groups, respectively). The change in 24-h nonprotein respiratory quotient from before to after treatment did not differ significantly between groups (0.009+-0.021 and 0.009+-0.029, respectively). No changes in glucose tolerance were observed, but triacylglycerol concentrations decreased significantly with L-796568 treatment compared with placebo (-0.76+-0.76 and 0.42+-0.31 mmol/L, respectively; P<0.002). Overall, treatment-related changes in body composition were not observed, but higher plasma L-796568 concentrations in the L-796568 group were associated with greater decreases in fat mass (r=-0.69, P<0.03). Conclusions: Treatment with L-796568 for 28 d had no major lipolytic or thermogenic effect but it lowered triacylglycerol concentrations. This lack of chronic effect on energy balance is likely explained by insufficient recruitment of beta3-responsive tissues in humans, down-regulation of the beta3-adrenergic receptor-mediated effects with chronic dosing, or both.
TI Effect of a 28-d treatment with L-796568, a novel beta3-adrenergic receptor agonist, on energy expenditure and body composition in obese men.
AB Background: Stimulation of energy expenditure (EE) with selective thermogenic beta-adrenergic agonists may be a promising approach for treating obesity. Objective: We analyzed the effects of the highly selective human beta3-adrenergic agonist L-796568 on 24-h EE, substrate oxidation, and body composition in obese, weight-stable men. Design: In this 2-center, double-blind, randomized, parallel-group study, we measured 24-h EE before and after 28 d of. . .
IT Major Concepts
Neurology (Human Medicine, Medical Sciences); Nutrition; Pharmacology
IT Diseases
obesity: nutritional disease, diet therapy, drug therapy
Obesity (MeSH)
IT Chemicals & Biochemicals
L-796568: adrenergic antagonist-drug, anorexic-drug, autonomic-drug, beta-adrenergic antagonist-drug, 28-day treatment, beta-3-adrenergic receptor agonist, thermogenic; beta-3-adrenergic receptor;. . .
RN 211031-81-1 (L-796568)

L9 ANSWER 4 OF 14 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2002:763926 CAPLUS
DN 137:288901
TI Effect of a 28-d treatment with L-796568, a novel β3-adrenergic receptor agonist, on energy expenditure and body composition in obese men
AU Larsen, Thomas M.; Toubro, Soren; van Baak, Marleen A.; Gottesdiener, Keith M.; Larson, Patrick; Saris, Wim H. M.; Astrup, Arne
CS Research Department of Human Nutrition, The Royal Veterinary and Agricultural University, Copenhagen, Den.
SO American Journal of Clinical Nutrition (2002), 76(4), 780-788
CODEN: AJCNAC; ISSN: 0002-9165
PB American Society for Clinical Nutrition
DT Journal
LA English
AB Stimulation of energy expenditure (EE) with selective thermogenic β-adrenergic agonists may be a promising approach for treating obesity. We analyzed the effects of the highly selective human β3-adrenergic agonist L-796568 on 24-h EE, substrate oxidation, and body composition in obese, weight-stable men. In this 2-center, double-blind, randomized, parallel-group study, we measured 24-h EE before and after 28 d of treatment with L-796568 (375 mg/d) or placebo during weight maintenance (ie, without dietary intervention) in nondiabetic, nonsmoking men aged 25-49 yr with body mass index (in kg/m2) of 28-35 (n = 10 subjects per treatment group). The mean change in 24-h EE from before to after treatment did not differ significantly between groups (92±586 and 86±512 kJ/24 h for the L-796568 and placebo groups, resp.). The change in 24-h nonprotein RQ from before to after treatment did not differ significantly between groups (0.009±0.021 and 0.009±0.029, resp.). No changes in glucose tolerance were observed, but triacylglycerol concns. decreased significantly with L-796568 treatment compared with placebo (-0.76±0.76 and 0.42±0.31 mmol/L, resp.; P < 0.002). Overall, treatment-related changes in body composition were not observed, but higher plasma L-796568 concns. in the L-796568 group were associated with greater decreases in fat mass (r = -0.69, P < 0.03). Treatment with L-796568 for 28 d had no major lipolytic or thermogenic effect but it lowered triacylglycerol concns. This lack of chronic effect on energy balance is likely explained by insufficient recruitment of β3-responsive tissues in humans, down-regulation of the β3-adrenergic receptor-mediated effects with chronic dosing, or both.
RE.CNT 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT
TI Effect of a 28-d treatment with L-796568, a novel β3-adrenergic receptor agonist, on energy expenditure and body composition in obese men
AB Stimulation of energy expenditure (EE) with selective thermogenic β-adrenergic agonists may be a promising approach for treating obesity. We analyzed the effects of the highly selective human β3-adrenergic agonist L-796568 on 24-h EE, substrate oxidation, and body composition in obese, weight-stable men. In this 2-center, double-blind, randomized, parallel-group study, we measured 24-h EE before and after 28 d of treatment with L-796568 (375 mg/d) or placebo during weight maintenance (ie, without dietary intervention) in nondiabetic, nonsmoking men aged 25-49 yr with body mass index (in kg/m2) of 28-35 (n = 10 subjects per treatment group). The mean change in 24-h EE from before to after treatment did not differ significantly between groups (92±586 and 86±512 kJ/24 h for the L-796568 and placebo groups, resp.). The change in 24-h nonprotein RQ from before to after treatment did not differ significantly between groups (0.009±0.021 and 0.009±0.029, resp.). No changes in glucose tolerance were observed, but triacylglycerol concns. decreased significantly with L-796568 treatment compared with placebo (-0.76±0.76 and 0.42±0.31 mmol/L, resp.; P < 0.002). Overall,

treatment-related changes in body composition were not observed, but higher plasma
L-796568 concns. in the L-796568 group were associated with greater decreases in fat mass (r = -0.69, P < 0.03). Treatment with L-796568 for 28 d had no major lipolytic or thermogenic effect but it lowered triacylglycerol concns. This lack of chronic effect on energy balance is likely explained by insufficient recruitment of β3-responsive tissues in humans, down-regulation of the β3-adrenergic receptor-mediated effects with chronic dosing, or both.

ST L796568 beta3 adrenergic receptor energy expenditure obese thermogenesis

IT Antiobesity agents
Energy metabolism, animal
Human
Obesity
Thermogenesis, biological
(effect of a 28-d treatment with L-796568, a novel β3-adrenergic receptor agonist, on energy expenditure and body composition in obese men)

IT Fatty acids, biological studies
Glycerides, biological studies
Lipolysis
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(effect of a 28-d treatment with L-796568, a novel β3-adrenergic receptor agonist, on energy expenditure and body composition in obese men)

IT Body weight
(lean; effect of a 28-d treatment with L-796568, a novel β3-adrenergic receptor agonist, on energy expenditure and body composition in obese men)

IT Adrenoceptor agonists
(β3-; effect of a 28-d treatment with L-796568, a novel β3-adrenergic receptor agonist, on energy expenditure and body composition in obese men)

IT 56-81-5, Glycerol, biological studies 57-88-5, Cholesterol, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(effect of a 28-d treatment with L-796568, a novel β3-adrenergic receptor agonist, on energy expenditure and body composition in obese men)

IT 211031-81-1, L-796568
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(effect of a 28-d treatment with L-796568, a novel β3-adrenergic receptor agonist, on energy expenditure and body composition in obese men)

L9 ANSWER 5 OF 14 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2002:363839 CAPLUS
DN 137:15695
TI Acute effect of L-796568, a novel β3-adrenergic receptor agonist, on energy expenditure in obese men
AU Van Baak, Marleen A.; Hul, Gabby B. J.; Toubro, Soren; Astrup, Arne; Gottesdiener, Keith M.; DeSmet, Marina; Saris, Wim H. M.
CS Nutrition and Toxicology Research Institute (NUTRIM), Maastricht University, Maastricht, 6200 MD, Neth.
SO Clinical Pharmacology & Therapeutics (St. Louis, MO, United States) (2002), 71(4), 272-279
CODEN: CLPTAT; ISSN: 0009-9236
PB Mosby, Inc.
DT Journal
LA English
AB Our objective was to investigate the thermogenic efficacy of single oral doses of the novel β3-adrenergic receptor agonist L-796568

[(R)-N-[4-[2-[[2-hydroxy-2-(3-pyridinyl) ethyl]amino]ethyl]-phenyl]
-4-[4-[4-(trifluoromethyl)phenyl] thiazol-2-yl]-benzenesulfonamide,
dihydrochloride] in humans. Twelve healthy overweight to obese
men participated in this 2-center, 3-period, randomized,
placebo-controlled, crossover trial. In each period subjects received 250
mg L-796568, 1000 mg L-796568, or placebo. Energy expenditure and RQ were
determined by indirect calorimetry; blood samples were taken; and ear
temperature,
heart rate, and blood pressure were measured at baseline and during the
4-h period after administration. Energy expenditure increased
significantly after the 1000-mg dose (about 8%) and this was accompanied
by an increase in plasma glycerol and free fatty acid concns. Systolic
blood pressure also increased significantly. No changes in heart rate,
diastolic blood pressure, ear temperature, plasma catecholamine, potassium, or
leptin were found. Single-dose administration of 1000 mg of the novel
β3-adrenergic receptor agonist L-796568 increased lipolysis and
energy expenditure in overweight men. This is the first study to show
such an effect of β3-adrenergic receptor agonists in humans without
significant evidence for β2-adrenergic receptor involvement.

RE.CNT 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

TI Acute effect of L-796568, a novel β3-adrenergic receptor agonist, on
energy expenditure in obese men

AB Our objective was to investigate the thermogenic efficacy of single oral
doses of the novel β3-adrenergic receptor agonist L-796568
[(R)-N-[4-[2-[[2-hydroxy-2-(3-pyridinyl) ethyl]amino]ethyl]-phenyl]
-4-[4-[4-(trifluoromethyl)phenyl] thiazol-2-yl]-benzenesulfonamide,
dihydrochloride] in humans. Twelve healthy overweight to obese
men participated in this 2-center, 3-period, randomized,
placebo-controlled, crossover trial. In each period subjects received 250
mg L-796568, 1000 mg L-796568, or placebo. Energy expenditure and RQ were
determined by indirect calorimetry; blood samples were taken; and ear
temperature,
heart rate, and blood pressure were measured at baseline and during the
4-h period after administration. Energy expenditure increased
significantly after the 1000-mg dose (about 8%) and this was accompanied
by an increase in plasma glycerol and free fatty acid concns. Systolic
blood pressure also increased significantly. No changes in heart rate,
diastolic blood pressure, ear temperature, plasma catecholamine, potassium, or
leptin were found. Single-dose administration of 1000 mg of the novel
β3-adrenergic receptor agonist L-796568 increased lipolysis and
energy expenditure in overweight men. This is the first study to show
such an effect of β3-adrenergic receptor agonists in humans without
significant evidence for β2-adrenergic receptor involvement.

ST L796568 adrenoceptor agonist antiobesity energy expenditure lipolysis
thermogenesis obesity

IT Antiobesity agents
Cardiovascular system
Energy metabolism, animal
Human
Thermogenesis, biological
(effect of L-796568, a novel β3-adrenergic receptor agonist, on
energy expenditure in obese men)

IT Fatty acids, biological studies
Lipolysis
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(effect of L-796568, a novel β3-adrenergic receptor agonist, on
energy expenditure in obese men)

IT Adrenoceptor agonists
(β3-; effect of L-796568, a novel β3-adrenergic receptor
agonist, on energy expenditure in obese men)

IT 211031-81-1, L 796568
RL: ADV (Adverse effect, including toxicity); DMA (Drug mechanism of
action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL

(Biological study); USES (Uses)
(effect of L-796568, a novel β3-adrenergic receptor agonist, on energy expenditure in obese men)

IT 56-81-5, Glycerol, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(effect of L-796568, a novel β3-adrenergic receptor agonist, on energy expenditure in obese men)

L9 ANSWER 6 OF 14 CAPLUS COPYRIGHT 2006 ACS on STN
AN 1998:527330 CAPLUS
DN 129:161557
TI Thiazole benzenesulfonamides as β3 agonists for the treatment of diabetes and obesity
IN Mathvink, Robert J.; Parmee, Emma R.; Tolman, Samuel; Weber, Ann E.
PA Merck & Co., Inc., USA
SO PCT Int. Appl., 64 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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	RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
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	AU 9860384	A1	19980818	AU 1998-60384	19980123
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	TR 9902442	T2	20000721	TR 1999-2442	19980123
	JP 2001509166	T2	20010710	JP 1998-532148	19980123
	ZA 9800647	A	19980728	ZA 1998-647	19980127
	NO 9903646	A	19990927	NO 1999-3646	19990727
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OS MARPAT 129:161557
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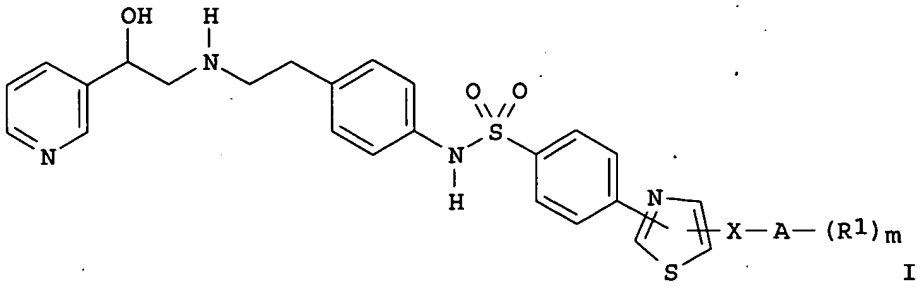

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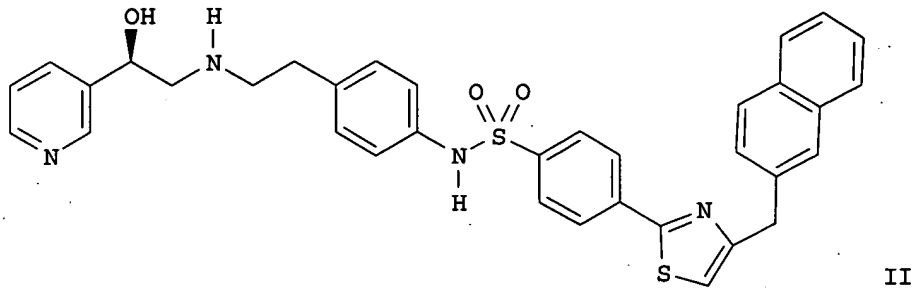

II

AB Thiazole-substituted benzenesulfonamides I [X = bond, C1-3 alkylene with optional Me or halo substituents or a contained O atom; m = 0-5; A = benzene, heterocycle, benzo-fused carbocycle, or hetero-fused carbo- or heterocycle; R1 = (un)substituted alkyl, cycloalkyl, oxo, halo, cyano, (un)substituted amino, CO2H or esters, etc.] and their prodrugs and pharmaceutically acceptable salts are disclosed. The compds. are β3 adrenergic receptor agonists (no data) with very little β1 and β2 adrenergic receptor activity, and as such are capable of increasing lipolysis and cellular energy expenditure. The compds. thus have potent activity in the treatment of Type II diabetes and obesity. The compds. can also be used to lower triglyceride levels and cholesterol levels or raise high d. lipoprotein levels, or to decrease gut motility. In addition, the compds. can be used to reduce neurogenic inflammation, or as antidepressants. Compns. and methods of use are also disclosed. The compds. are prepared, e.g., by coupling an aminoalkylphenyl-sulfonamide with an appropriately substituted epoxide. Alternatively, for instance, 2-naphthylmethyl chloromethyl ketone was cyclized with 4-bromothiobenzamide to give 2-(4-bromophenyl)-4-(2-naphthylmethyl)thiazole. The latter bromide was lithiated and then treated with SO2 followed by NCS to give the corresponding sulfonyl chloride. Amidation of this with the corresponding enantiomeric amine gave title compound II.

RE.CNT 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

TI Thiazole benzenesulfonamides as β3 agonists for the treatment of diabetes and obesity

AB Thiazole-substituted benzenesulfonamides I [X = bond, C1-3 alkylene with optional Me or halo substituents or a contained O atom; m = 0-5; A = benzene, heterocycle, benzo-fused carbocycle, or hetero-fused carbo- or heterocycle; R1 = (un)substituted alkyl, cycloalkyl, oxo, halo, cyano, (un)substituted amino, CO2H or esters, etc.] and their prodrugs and pharmaceutically acceptable salts are disclosed. The compds. are β3 adrenergic receptor agonists (no data) with very little β1 and β2 adrenergic receptor activity, and as such are capable of increasing lipolysis and cellular energy expenditure. The compds. thus have potent activity in the treatment of Type II diabetes and obesity. The compds. can also be used to lower triglyceride levels and cholesterol levels or raise high d. lipoprotein levels, or to decrease gut motility. In addition, the compds. can be used to reduce

neurogenic inflammation, or as antidepressants. Compns. and methods of use are also disclosed. The compds. are prepared, e.g., by coupling an aminoalkylphenyl-sulfonamide with an appropriately substituted epoxide. Alternatively, for instance, 2-naphthylmethyl chloromethyl ketone was cyclized with 4-bromothiobenzamide to give 2-(4-bromophenyl)-4-(2-naphthylmethyl)thiazole. The latter bromide was lithiated and then treated with SO2 followed by NCS to give the corresponding sulfonyl chloride. Amidation of this with the corresponding enantiomeric amine gave title compound II.

IT 211030-99-8P 211031-01-5P 211031-03-7P 211031-05-9P 211031-07-1P
211031-09-3P 211031-11-7P 211031-13-9P 211031-15-1P 211031-17-3P
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211032-55-2P 211032-57-4P 211032-59-6P 211032-61-0P 211032-64-3P
211032-67-6P 211032-70-1P 211032-73-4P 211032-75-6P 211032-78-9P
211032-81-4P 211032-84-7P 211032-87-0P 211032-89-2P 211032-91-6P
211032-93-8P 211032-95-0P 211032-97-2P 211033-00-0P 211033-03-3P
211033-05-5P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of thiazole benzenesulfonamides as β3 agonists)

L9 ANSWER 7 OF 14 Elsevier BIOBASE COPYRIGHT 2006 Elsevier Science B.V. on STN

AN 2002219708 ESBIOBASE

TI Effect of a 28-d treatment with L-796568, a novel β.sub.3-adrenergic receptor agonist, on energy expenditure and body composition in obese men

AU Larsen T.M.; Toubro S.; Van Baak M.A.; Gottesdiener K.M.; Larson P.; Saris W.H.M.; Astrup A.

CS T.M. Larsen, Res. Department of Human Nutrition, Roy. Vet./Agricultural University, Rolighedsvej 30, 1958 Frederiksberg, Copenhagen, Denmark. E-mail: tml@kvl.dk

SO American Journal of Clinical Nutrition, (2002), 76/4 (780-788), 45 reference(s)
CODEN: AJCNAC ISSN: 0002-9165

DT Journal; Article

CY United States

LA English

SL English

AB Background: Stimulation of energy expenditure (EE) with selective thermogenic β-adrenergic agonists may be a promising approach for treating obesity. Objective: We analyzed the effects of the highly selective human β-adrenergic agonist L-796568 on 24-h EE, substrate oxidation, and body composition in obese, weight-stable men. Design: In this 2-center, double-blind, randomized, parallel-group study, we measured 24-h EE before and after 28 d of treatment with L-796568 (375 mg/d) or placebo during weight maintenance (ie, without dietary intervention) in nondiabetic, nonsmoking men aged 25-49 y with body mass index (in kg/m.sup.2) of 28-35 (n = 10 subjects per treatment group). Results: The mean change in 24-h EE from before to after treatment did not differ significantly between groups (92 ± 586 and 86 ± 512 kJ/24 h for the L-796568 and placebo groups, respectively). The change

in 24-h nonprotein respiratory quotient from before to after treatment did not differ significantly between groups (0.009 ± 0.021 and 0.009 ± 0.029, respectively). No changes in glucose tolerance were observed, but triacylglycerol concentrations decreased significantly with L -796568 treatment compared with placebo (-0.76 ± 0.76 and 0.42 ± 0.31 mmol/L, respectively; P < 0.002). Overall, treatment-related changes in body composition were not observed, but higher plasma L-796568 concentrations in the L-796568 group were associated with greater decreases in fat mass (r = -0.69, P < 0.03). Conclusions: Treatment with L -796568 for 28 d had no major lipolytic or thermogenic effect but it lowered triacylglycerol concentrations. This lack of chronic effect on energy balance is likely explained by insufficient recruitment of β.sub.3-responsive tissues in humans, down-regulation of the β.sub.3-adrenergic receptor-mediated effects with chronic dosing, or both.

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ST L-796568; β.sub.3-adrenergic receptor; β.sub.3-adrenergic receptor agonist; β.sub.3 agonist; Selectivity; Energy expenditure; Lipolysis; Respiratory quotient; Indirect calorimetry; Triacylglycerol; Obesity; Obese men

L9 ANSWER 8 OF 14 PASCAL on STN

AN 2002-0579884 PASCAL

TIEN Effect of a 28-d treatment with L-796568, a novel β.sub.3-adrenergic receptor agonist, on energy expenditure and body composition in obese men

AU LARSEN Thomas M.; TOUBRO Soren; VAN BAAK Marleen A.; GOTTESDIENER Keith M.; LARSON Patrick; SARIS Wim H. M.; ASTRUP Arne

CS Research Department of Human Nutrition, The Royal Veterinary and Agricultural University, Copenhagen, Denmark; Nutrition and Toxicology Research Institute (NUTRIM), Department of Human Biology, Maastricht University, Maastricht, Netherlands; Merck & Co, Rahway, NJ, United States

SO The American journal of clinical nutrition, (2002), 76(4), 780-788, 45 refs.
ISSN: 0002-9165 CODEN: AJCNAC
DT Journal
BL Analytic
CY United States
LA English
AV INIST-8263, 354000109283810130

AB Background: Stimulation of energy expenditure (EE) with selective thermogenic β-adrenergic agonists may be a promising approach for treating obesity. Objective: We analyzed the effects of the highly selective human β.sub.3-adrenergic agonist L-796568 on 24-h EE, substrate oxidation, and body composition in obese, weight-stable men. Design: In this 2-center, double-blind, randomized, parallel-group study, we measured 24-h EE before and after 28 d of treatment with L-796568 (375 mg/d) or placebo during weight maintenance (ie, without dietary intervention) in nondiabetic, nonsmoking men aged 25-49 y with body mass index (in kg/m.sup.2) of 28-35 (n = 10 subjects per treatment group). Results: The mean change in 24-h EE from before to after treatment did not differ significantly between groups (92 ± 586 and 86 ± 512 kJ/24 h for the L-796568 and placebo groups, respectively). The change in 24-h nonprotein respiratory quotient from before to after treatment did not differ significantly between groups (0.009 ± 0.021 and 0.009 ± 0.029, respectively). No changes in glucose tolerance were observed, but triacylglycerol concentrations decreased significantly with L-796568 treatment compared with placebo (-0.76 ± 0.76 and 0.42 ± 0.31 mmol/L, respectively; P < 0.002). Overall, treatment-related changes in body composition were not observed, but higher plasma L-796568 concentrations in the L-796568 group were associated with greater decreases in fat mass (r = -0.69, P < 0.03). Conclusions: Treatment with L-796568 for 28 d had no major lipolytic or thermogenic effect but it lowered triacylglycerol concentrations. This lack of chronic effect on energy balance is likely explained by insufficient recruitment of β.sub.3-responsive tissues in humans, down-regulation of the β.sub.3-adrenergic receptormediated effects with chronic dosing, or both.
TIEN Effect of a 28-d treatment with L-796568, a novel β.sub.3-adrenergic receptor agonist, on energy expenditure and body composition in obese men
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-796568 for 28 d had no major lipolytic or thermogenic effect but it lowered triacylglycerol concentrations. This lack of chronic effect. . .

CT Agonist; β3-Adrenergic receptor; Treatment; Energetic cost; Body composition; Anthropometry; Indirect calorimetry; Obesity; Nutritional status; Respiratory quotient; Randomized design; Double blind study; Human; Male

L9 ANSWER 9 OF 14 PASCAL on STN

AN 2002-0455153 PASCAL

CP

TIEN Acute effect of L-796568, a novel β.sub.3-adrenergic receptor agonist, on energy expenditure in obese men

AU VAN BAAK Marleen A.; HUL Gabby B. J.; TOUBRO Siren; ASTRUP Arne; GOTTESDIENER Keith M.; DESMET Marina; SARIS Wim H. M.

CS Nutrition and Toxicology Research Institute (NUTRIM), Department of Human Biology, Maastricht University, Netherlands; Research Department of Human Nutrition, Royal Veterinary and Agricultural University, Copenhagen, Denmark; Merck & Co. Inc., Rahway, NJ, United States

SO Clinical pharmacology and therapeutics, (2002), 71(4), 272-279, 34 refs. ISSN: 0009-9236 CODEN: CLPTAT

DT Journal

BL Analytic

CY United States

LA English

AV INIST-1144, 354000108249030090

CP

AB Objective: Our objective was to investigate the thermogenic efficacy of single oral doses of the novel β.sub.3-adrenergic receptor agonist L-796568 [(R)-N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]-phenyl]-4-[4- [4-(trifluoromethyl)phenyl]thiazol-2-yl]-benzenesulfonamide, dihydrochloride] in humans. Methods: Twelve healthy overweight to obese men participated in this 2-center, 3-period, randomized, placebo-controlled, crossover trial. In each period subjects received 250 mg L-796568, 1000 mg L-796568, or placebo. Energy expenditure and respiratory quotient were determined by indirect calorimetry; blood samples were taken; and ear temperature, heart rate, and blood pressure were measured at baseline and during the 4-hour period after administration. Results: Energy expenditure increased significantly after the 1000-mg dose (about 8%) and this was accompanied by an increase in plasma glycerol and free fatty acid concentrations. Systolic blood pressure also increased significantly. No changes in heart rate, diastolic blood pressure, ear temperature, plasma catecholamine, potassium, or leptin were found. Conclusions: Single-dose administration of 1000 mg of the novel β.sub.3-adrenergic receptor agonist L-796568 increased lipolysis and energy expenditure in overweight men. This is the first study to show such an effect of β.sub.3-adrenergic receptor agonists in humans without significant evidence for β.sub.2-adrenergic receptor involvement.

TIEN Acute effect of L-796568, a novel β.sub.3-adrenergic receptor agonist, on energy expenditure in obese men

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CT Obesity; β3-Adrenergic receptor; Agonist; Energy; Expenditure; Biological activity; Single dose; Oral administration; Controlled therapeutic trial; Human; Hemodynamics; Body temperature; Lipolysis; Treatment;. . .

CTFR. . . Energie; Depense; Activite biologique; Dose unique; Voie orale; Essai therapeutique controle; Homme; Hemodynamique; Temperature corporelle; Lipolyse; Traitement; Chimiotherapie; Etat nutritionnel; L 796568

L9 ANSWER 10 OF 14 SCISEARCH COPYRIGHT (c) 2006 The Thomson Corporation on STN

AN 2002:783618 SCISEARCH

GA The Genuine Article (R) Number: 595GV

TI Effect of a 28-d treatment with L-796568, a novel beta(3)-adrenergic receptor agonist, on energy expenditure and body composition in obese men

AU Larsen T M (Reprint); Toubro S; van Baak M A; Gottesdiener K M; Larson P; Saris W H M; Astrup A

CS Royal Vet & Agr Univ, Res Dept Human Nutr, Rolighedsvej 30, DK-1958 Frederiksberg, Denmark (Reprint); Royal Vet & Agr Univ, Res Dept Human Nutr, DK-1958 Frederiksberg, Denmark; Maastricht Univ, Nutr & Toxicol Res Inst NUTRIM, Dept Human Biol, Maastricht, Netherlands; Merck & Co Inc, Rahway, NJ 07065 USA

CYA Denmark; Netherlands; USA

SO AMERICAN JOURNAL OF CLINICAL NUTRITION, (OCT 2002) Vol. 76, No. 4, pp. 780-788.
ISSN: 0002-9165.

PB AMER SOC CLINICAL NUTRITION, 9650 ROCKVILLE PIKE, SUBSCRIPTIONS, RM L-3300, BETHESDA, MD 20814-3998 USA.

DT Article; Journal

LA English

REC Reference Count: 45

ED Entered STN: 18 Oct 2002
Last Updated on STN: 18 Oct 2002

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Background: Stimulation of energy expenditure (EE) with selective thermogenic P-adrenergic agonists may be a promising approach for treating obesity.

Objective: We analyzed the effects of the highly selective human beta(3)-adrenergic agonist L-796568 on 24-h EE, substrate oxidation, and body composition in obese, weight-stable men.

Design: In this 2-center, double-blind, randomized, parallel-group study, we measured 24-h EE before and after 28 d of treatment with L-796568 (375 mg/d) or placebo during weight maintenance (ie, without dietary intervention) in nondiabetic, nonsmoking men aged 25-49 y with body mass index (in kg/m(2)) of 28-35 (n = 10 subjects per treatment group).

Results: The mean change in 24-h EE from before to after treatment did not differ significantly between groups (92 586 and 86 512 kJ/24 h for the L-796568 and placebo groups, respectively). The change in 24-h nonprotein respiratory quotient from before to after treatment did not differ significantly between groups (0.009 +/- 0.021 and 0.009 +/- 0.029, respectively). No changes in glucose tolerance were observed, but triacylglycerol concentrations decreased significantly with L-796568 treatment compared with placebo (-0.76 +/- 0.76 and 0.42 +/- 0.31 mmol/L, respectively; P < 0.002). Overall,

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Conclusions: Treatment with L-796568 for 28 d had no major lipolytic or thermogenic effect but it lowered triacylglycerol concentrations. This lack of chronic effect on energy balance is likely explained by insufficient recruitment of beta(3)-responsive tissues in humans, down-regulation of the beta(3)-adrenergic receptormediated effects with chronic dosing, or both.

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Conclusions: Treatment with L-796568 for 28 d had no major lipolytic or thermogenic effect but it lowered triacylglycerol concentrations. This lack of chronic effect. . .

ST Author Keywords: L-796568; beta(3)-adrenergic receptor; beta(3)-adrenergic receptor agonist; beta(3) agonist; selectivity; energy expenditure; lipolysis; respiratory quotient; indirect calorimetry; triacylglycerol; obesity; obese men

L9 ANSWER 11 OF 14 SCISEARCH COPYRIGHT (c) 2006 The Thomson Corporation on STN

AN 2002:353227 SCISEARCH

GA The Genuine Article (R) Number: 543XN

TI Acute effect of L-796568, a novel beta(3)-adrenergic receptor agonist, on energy expenditure in obese men

AU van Baak M A (Reprint); Hul G B J; Toubro S; Astrup A; Gottesdiener K M; DeSmet M; Saris W H M

CS Maastricht Univ, Dept Human Biol, Nutr & Toxicol Res Inst, POB 616, NL-6200 MD Maastricht, Netherlands (Reprint); Maastricht Univ, Dept Human Biol, Nutr & Toxicol Res Inst, NL-6200 MD Maastricht, Netherlands; Royal Vet & Agr Univ, Res Dept Human Nutr, Copenhagen, Denmark; Merck & Co Inc, Rahway, NJ 07065 USA

CYA Netherlands; Denmark; USA

SO CLINICAL PHARMACOLOGY & THERAPEUTICS, (APR 2002) Vol. 71, No. 4, pp. 272-279.
ISSN: 0009-9236.

PB MOSBY, INC, 11830 WESTLINE INDUSTRIAL DR, ST LOUIS, MO 63146-3318 USA.

DT Article; Journal

LA English

REC Reference Count: 34
ED Entered STN: 10 May 2002
Last Updated on STN: 10 May 2002
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Objective: Our objective was to investigate the thermogenic efficacy of single oral doses of the novel beta(3)-adrenergic receptor agonist L-796568 [(R)-N-[4-[2-[[2-hydroxy-2-(3-pyridinyl)ethyl]amino]ethyl]phenyl]-4-[4-[4-(trifluoromethyl)phenyl]thiazol-2-yl]-benzenesulfonamide, dihydrochloride] in humans.

Methods: Twelve healthy overweight to obese men participated in this 2-center, 3-period, randomized, placebo-controlled, crossover trial. In each period subjects received 250 mg L-796568, 1000 mg L-796568, or placebo. Energy expenditure and respiratory quotient were determined by indirect calorimetry; blood samples were taken; and ear temperature, heart rate, and blood pressure were measured at baseline and during the 4-hour period after administration.

Results: Energy expenditure increased significantly after the 1000-mg dose (about 8%) and this was accompanied by an increase in plasma glycerol and free fatty acid concentrations. Systolic blood pressure also increased significantly. No changes in heart rate, diastolic blood pressure, ear temperature, plasma catecholamine, potassium, or leptin were found.

Conclusions: Single-dose administration of 1000 mg of the novel beta(3)-adrenergic receptor agonist L-796568 increased lipolysis and energy expenditure in overweight men. This is the first study to show such an effect of beta(3)-adrenergic receptor agonists in humans without significant evidence for beta(2)-adrenergic receptor involvement.

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L9 ANSWER 12 OF 14 SCISEARCH COPYRIGHT (c) 2006 The Thomson Corporation on STN
AN 2000:859460 SCISEARCH
GA The Genuine Article (R) Number: 364DE
TI Acute thermogenic effect of L-796568, a novel beta(3)-adrenoceptor agonist, in obese men
AU van Baak M A (Reprint); Hul G; Toubro S; Astrup A; Gottesdiener K M; DeSmer M; Saris W H M
CS Maastricht Univ, Maastricht, Netherlands; Royal Vet & Agr Univ, Copenhagen, Denmark; Merck & Co Inc, Rahway, NJ 07065 USA
CYA Netherlands; Denmark; USA
SO OBESITY RESEARCH, (OCT 2000) Vol. 8, Supp. [1], pp. 91S-91S. MA PB95. ISSN: 1071-7323.
PB NORTH AMER ASSOC STUDY OBESITY, 8630 FENTON ST, SUITE 918, SILVER SPRING, MD 20910 USA.
DT Conference; Journal

LA English
REC Reference Count: 0
ED Entered STN: 2000
Last Updated on STN: 2000
TI Acute thermogenic effect of L-796568, a novel beta(3)-adrenoceptor agonist, in obese men

L9 ANSWER 13 OF 14 TOXCENTER COPYRIGHT 2006 ACS on STN
AN 2002:147486 TOXCENTER
CP Copyright 2006 ACS
DN CA13702015695B
TI Acute effect of L-796568, a novel β3-adrenergic receptor agonist, on energy expenditure in obese men
AU Van Baak, Marleen A.; Hul, Gabby B. J.; Toubro, Soren; Astrup, Arne; Gottesdiener, Keith M.; DeSmet, Marina; Saris, Wim H. M.
CS Nutrition and Toxicology Research Institute (NUTRIM), Maastricht University, Maastricht, 6200 MD, Neth..
SO Clinical Pharmacology & Therapeutics (St. Louis, MO, United States), (2002) Vol. 71, No. 4, pp. 272-279.
CODEN: CLPTAT. ISSN: 0009-9236.
CY NETHERLANDS
DT Journal
FS CAPLUS
OS CAPLUS 2002:363839
LA English
ED Entered STN: 2 Jul 2002
Last Updated on STN: 2 May 2006
AB Our objective was to investigate the thermogenic efficacy of single oral doses of the novel β3-adrenergic receptor agonist L-796568 [(R)-N-[4-[2-[[2-hydroxy-2-(3-pyridinyl) ethyl]amino]ethyl]-phenyl] -4-[4-[4-(trifluoromethyl)phenyl] thiazol-2-yl]-benzenesulfonamide, dihydrochloride] in humans. Twelve healthy overweight to obese men participated in this 2-center, 3-period, randomized, placebo-controlled, crossover trial. In each period subjects received 250 mg L-796568, 1000 mg L-796568, or placebo. Energy expenditure and RQ were determined by indirect calorimetry; blood samples were taken; and ear temperature, heart rate, and blood pressure were measured at baseline and during the 4-h period after administration. Energy expenditure increased significantly after the 1000-mg dose (about 8%) and this was accompanied by an increase in plasma glycerol and free fatty acid concns. Systolic blood pressure also increased significantly. No changes in heart rate, diastolic blood pressure, ear temperature, plasma catecholamine, potassium, or leptin were found. Single-dose administration of 1000 mg of the novel β3-adrenergic receptor agonist L-796568 increased lipolysis and energy expenditure in overweight men. This is the first study to show such an effect of β3-adrenergic receptor agonists in humans without significant evidence for β2-adrenergic receptor involvement.
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ST Miscellaneous Descriptors
L796568 adrenoceptor agonist antiobesity energy expenditure lipolysis thermogenesis obesity
RN 211031-81-1 (L 796568)
56-81-5 (Glycerol)

L9 ANSWER 14 OF 14 USPATFULL on STN

AN 2000:1891 USPATFULL
TI Thiazole benzenesulfonamides as β3 agonists for treatment of diabetes and obesity
IN Mathvink, Robert J., Red Bank, NJ, United States
Parmee, Emma R., Highland Park, NJ, United States
Tolman, Samuel, Jersey City, NJ, United States
Weber, Ann E., Scotch Plains, NJ, United States
PA Merck & Co., Inc., Rahway, NJ, United States (U.S. corporation)
PI US 6011048 20000104
AI US 1998-7363 19980115 (9)
PRAI US 1997-36760P 19970128 (60)
DT Utility
FS Granted
EXNAM Primary Examiner: Fan, Jane
LREP Yang, Mollie M., Rose, David L.
CLMN Number of Claims: 10
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 1510
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Thiazole substituted benzenesulfonamides are β.sub.3 adrenergic receptor agonists with very little β.sub.1 and β.sub.2 adrenergic receptor activity and as such the compounds are capable of increasing lipolysis and energy expenditure in cells. The compounds thus have potent activity in the treatment of Type II diabetes and obesity. The compounds can also be used to lower triglyceride levels and cholesterol levels or raise high density lipoprotein levels or to decrease gut motility. In addition, the compounds can be used to reduced neurogenic inflammation or as antidepressant agents. The compounds are prepared by coupling an aminoalkylphenyl-sulfonamide with an appropriately substituted epoxide. Compositions and methods for the use of the compounds in the treatment of diabetes and obesity and for lowering triglyceride levels and cholesterol levels or raising high density lipoprotein levels or for decreasing gut motility are also disclosed.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
TI Thiazole benzenesulfonamides as β3 agonists for treatment of diabetes and obesity
AB . . . lipolysis and energy expenditure in cells. The compounds thus have potent activity in the treatment of Type II diabetes and obesity. The compounds can also be used to lower triglyceride levels and cholesterol levels or raise high density lipoprotein levels or. . . with an appropriately substituted epoxide. Compositions and methods for the use of the compounds in the treatment of diabetes and obesity and for lowering triglyceride levels and cholesterol levels or raising high density lipoprotein levels or for decreasing gut motility are. . .
SUMM . . . present invention are useful in treating or preventing include, but are not limited to, (1) diabetes mellitus, (2) hyperglycemia, (3) obesity, (4) hyperlipidemia, (5) hypertriglyceridemia, (6) hypercholesterolemia, (7) atherosclerosis of coronary, cerebrovascular and peripheral arteries, (8) gastrointestinal disorders including peptid ulcer,. . .
SUMM When treating obesity (in conjunction with diabetes and/or hyperglycemia, or alone) in human or non-human animals such as dogs and cats, generally satisfactory. . .
CLM What is claimed is:
9. A composition for the treatment of diabetes or obesity or for lowering triglyceride or cholesterol levels or increasing high density lipoprotein levels or for decreasing gut motility or for. . .
IT 211030-99-8P 211031-01-5P 211031-03-7P 211031-05-9P 211031-07-1P
211031-09-3P 211031-11-7P 211031-13-9P 211031-15-1P 211031-17-3P
211031-19-5P 211031-21-9P 211031-23-1P 211031-25-3P 211031-27-5P

211031-29-7P 211031-31-1P 211031-33-3P 211031-35-5P 211031-37-7P
211031-39-9P 211031-41-3P 211031-43-5P 211031-45-7P 211031-47-9P
211031-49-1P 211031-51-5P 211031-53-7P 211031-55-9P 211031-57-1P
211031-59-3P 211031-61-7P 211031-63-9P 211031-65-1P 211031-67-3P
211031-69-5P 211031-71-9P 211031-73-1P 211031-75-3P 211031-77-5P
211031-79-7P 211031-81-1P 211031-83-3P 211031-85-5P
211032-15-4P 211032-17-6P 211032-19-8P 211032-21-2P 211032-23-4P
211032-25-6P 211032-27-8P 211032-29-0P 211032-31-4P 211032-33-6P
211032-35-8P 211032-37-0P 211032-39-2P 211032-41-6P 211032-43-8P
211032-45-0P 211032-47-2P 211032-49-4P 211032-51-8P 211032-53-0P
211032-55-2P 211032-57-4P 211032-59-6P 211032-61-0P 211032-64-3P
211032-67-6P 211032-70-1P 211032-73-4P 211032-75-6P 211032-78-9P
211032-81-4P 211032-84-7P 211032-87-0P 211032-89-2P 211032-91-6P
211032-93-8P 211032-95-0P 211032-97-2P 211033-00-0P 211033-03-3P
211033-05-5P
(preparation of thiazole benzenesulfonamides as β3 agonists)

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